REMARKS

This Supplemental Amendment is submitted in response to the interview held with the Examiner on November 4, 2011. It is Applicants' understanding that the After Final Amendment submitted on August 19, 2011, was entered with the filing of the Request for Continued Examination on October 18, 2011 and that this Supplemental Amendment will be considered with the Amendment previously submitted on August 19, 2011, and entered on October 18, 2011. Accordingly, Applicants are not resubmitting the section of the previous Amendment entitled "Remarks."

Interview Summary

Applicants would like to thank Examiner Schultz for the interview held on November 4, 2011. During the interview, the cited references were discussed. Applicants filed a Request for Continued Examination on October 18, 2011, and requested the entry of the After Final Amendment previously submitted on August 19, 2011. Examiner stated that he will review the cited references in view of the amendments and remarks submitted in the After Final Amendment. Examiner suggested the filing of a Supplemental Amendment, if there are additional changes to the claims that Applicants would like to make prior to the Examiner acting on the application.

Applicants note that the interview was held on November 4, 2011, instead of October 4, 2011, as indicated on the Interview Summary, dated November 15, 2011.

Status of the Claims

Claims 36, 39, 44-69, 72-76, and 80-90 are currently pending. Claims 1-35, 37-43, 70, 71, and 77-79 have been canceled without prejudice or disclaimer of the subject matter claimed therein. Claims 64-66 are withdrawn from consideration as being directed to a non-elected species. Claims 36, 44-45, 52, 55, 57-59, 64-66, 68, and 69 have been amended. New claims 80-90, directed to the same invention as currently pending claims under examination, have been added.

In this Supplemental Amendment, Applicants have canceled claims 39, 42, and 43, solely to advance prosecution. The cancelation of claims 39, 42, and 43 do not alter the scope of the pending claims.

Representative support for the amendments to claims 36, 44-45, 52, 55, 57-59, 64-66, 68, and 69 can be found in their respective claims as originally filed.

Representative support for new claims 80-90 can be found in claims 59, 62, and 63 as originally filed.

The amendments to the claims and the addition of the new claims do not introduce prohibited new matter.

Reference

Applicants provide the attached reference, Lohr (Lohr *et al.,* Annals of Oncology, 2011, online publication) for Examiner's consideration. As explained in the reference of Lohr, the standard therapy for patients with advanced pancreatic cancer is chemotherapy with gemcitabine. The average survival of these patients is about 6 months. To improve survival rates, gemcitabine based combination therapy has been tested.

Lohr discloses the results of a phase II trial involving treating patients suffering from pancreatic cancer with a combination of gemcitabine and a low dosage paclitaxel. Like the present invention, the paclitaxel is embedded in cationic liposomes and administered to the patient as a cationic liposomal paclitaxel composition called EndoTAG^{TM}-1 (ET).

In the phase II trial conducted by Lohr, patients were administered gemcitabine alone, gemcitabine and 11 mg/m^2 of ET, gemcitabine and 22 mg/m^2 of ET, or gemcitabine and 44 mg/m^2 of ET. The results of the phase II trial are discussed in detail in the paper. Lohr reported that the low dosages of paclitaxel were well tolerated by the patients and prolonged the survival of patients (see for example Figure 3).

As explained in the response submitted on August 19, 2011, the conversion of mg/m^2 of paclitaxel to mg/kg of paclitaxel can be performed using the Food and Drug Administration (FDA) dose calculator available at http://www.accessdata.fda.gov/scripts/cder/onctools/animalquery.cfm. The conversion of the dosages used by Lohr to mg/kg bodyweight for a human is summarized in the table below.

FDA Dose Calculator Results (see attached)

Species	Weight (kg)	Dose (mg/kg)	Dose (mg/m^2)
Human	70	0.28	11
Human	70	0.56	22
Human	70	1.13	44

Applicants submit that Lohr shows that low dosages of paclitaxel, as claimed in the present invention, are effective in treating human patients.

As discussed in the response submitted on August 19, 2011, prior to the present invention, Rahman and other groups taught using high doses of paclitaxel, ranging from 50 mg/m^2 to 300 mg/m^2, to eradicate tumor cells as quickly and completely as possible. Accordingly, the present invention provides a novel method and unobvious method of treating patients. The cited references of McDonald and Rahman do not render the claimed invention obvious.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration, and the timely allowance of the pending claims. A favorable action is awaited. Should an interview be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 13-3250. If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: a randomized controlled phase II trial

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Background: Paclitaxel embedded in cationic liposomes (EndoTAG™-1; ET) is an innovative agent targeting tumor endothelial cells. This randomized controlled phase II trial evaluated the safety and efficacy of ET in combination with gemcitabine (GEM) in advanced pancreatic cancer (PDAC).

Patients and methods: Chemotherapy-naive patients with locally advanced or metastatic disease were randomly assigned to receive weekly GEM 1000 mg/m^2 or GEM plus twice-weekly ET 11, 22 or 44 mg/m^2 for 7 weeks. After a safety run-in of 100 patients, a second cohort continued treatment. End points included overall survival (OS), progression-free survival (PFS), tumor response and safety.

Results: Two hundred and twelve patients were randomly allocated to the study and 200 were treated (80% metastatic, 20% locally advanced). Adverse events were manageable and reversible. Transient thrombocytopenia and infusion reactions with chills and pyrexia mostly grade 1 or 2 occurred in the ET groups. Disease control rate after the first treatment cycle was 43% with GEM and 60%, 65% and 52% in the GEM + ET cohorts. Median PFS reached 2.7 compared with 4.1, 4.6 and 4.4 months, respectively. Median OS was 6.8 compared with 8.1, 8.7 and 9.3 months, respectively.

Conclusions: Treatment of advanced PDAC with GEM + ET was generally well tolerated. GEM + ET showed beneficial survival and efficacy. A randomized phase III trial should confirm this positive trend.

Key words: cationic liposomes, EndoTAG™-1, liposomal paclitaxel, pancreatic cancer, vascular targeting

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introduction

Pancreatic cancer (PDAC) is the fourth most common cause of cancer-related death in the Western world, with an estimated 36 800 deaths in the United States in 2010 [1]. Less than 20% of PDAC patients are diagnosed with resectable and potentially curable disease; usually patients have advanced disease at the time of diagnosis [2, 3].

Gemcitabine (GEM) has been the standard systemic therapy for palliative treatment of advanced PDAC during the last decade, with a median survival of ~6 months and 1-year survival rates of ~18% [4, 5]. Numerous phase III trials failed to demonstrate superiority of combinations of GEM with other agents [6, 7]. Only the combination with erlotinib achieved a modest but statistically significant improvement of survival and was approved in this indication [4, 5]. Due to the poor prognosis and limited treatment options, there is a high medical need for the development of new therapies.

Treatment with taxanes was examined in several studies with good tolerability. Docetaxel was judged to be active in untreated patients in a phase II trial [8], also after pretreatment [9]. Paclitaxel has been proven to be safe but was considered moderately effective, even in recent studies [10, 11].

Angiogenesis is essential for growth and metastasis of most solid malignancies. While not grossly vascular, pancreatic

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adenocarcinoma exhibits foci of micro-angiogenesis and overexpresses multiple pro-angiogenic factors [12, 13]. EndoTAG™-1 (ET) is a novel formulation of charged liposomes, carrying paclitaxel embedded in the cationic liposome membrane. Tumor endothelia lack the glycocalix usually covering endothelia under normal conditions, thus exposing the negatively charged cell surface. Through this mechanism, positively charged liposomes can selectively bind to tumor endothelial cells and internalize after i.v. administration [14–17] (Figure 1). Paclitaxel is thereby selectively delivered to the activated intratumoral endothelial cells [18]. These targeting properties and antitumor effects of ET have been demonstrated in animal models including orthotopic pancreatic carcinoma [18–20].

Several phase I studies demonstrate an acceptable safety profile and antitumor activity of ET in patients with different solid tumors (MediGene on file). The present trial was conducted to evaluate the safety and efficacy of ET at three different dose levels in combination with GEM in patients with locally advanced or metastatic adenocarcinoma of the pancreas, with GEM monotherapy used to define the patient cohort.

patients and methods

study design and treatment

This trial was an open-label, randomized, controlled, multicenter phase II study. Patients were randomly assigned to one of the four treatment groups: gemcitabine monotherapy or gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel (ET; GEM + Endo11), 22 mg/m^2 (GEM + Endo22) or 44 mg/m^2 (GEM + Endo44). Patients were centrally randomized. Due to the characteristic application schedule of ET, a blinded study design was not appropriate.

Treatment consisted of 7 weekly infusions of GEM (1000 mg/m^2/30 min) on days 4, 11, etc. and, if applicable, 14 twice-weekly infusions of ET on days 1, 4, etc. (10 min at 0.5 ml/min, 10 min at 1.0 ml/min and thereafter 1.5 ml/min). Treatment was administered for one complete cycle unless there was documented disease progression, unacceptable toxicity or patient refusal. Premedication was optional. In the event of toxic effects, treatment with study medication was delayed or GEM was administered at a reduced dose (80%) depending on the severity of the toxicity. Dose reductions for ET were not permitted.

After enrollment of 100 patients, the protocol was amended to allow continued treatment with ET in the GEM + Endo groups. Further antitumor therapy after discontinuation of study medication was at the discretion of the investigator.

patient characteristics

Eligibility criteria were age ≥18 years; histologically or cytologically confirmed unresectable locally advanced or metastatic ductal adenocarcinoma of the exocrine pancreas suitable for chemotherapy; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of two or less; adequate renal, hepatic and cardiac function; adequate bone marrow reserve (white blood cells > 3 × 10^3/mm^3, absolute neutrophil count > 1.5 × 10^3/mm^3, platelets > 100 000/mm^3, hemoglobin > 9.0 g/dl); bilirubin two times or less the upper limit of normal. Patients were

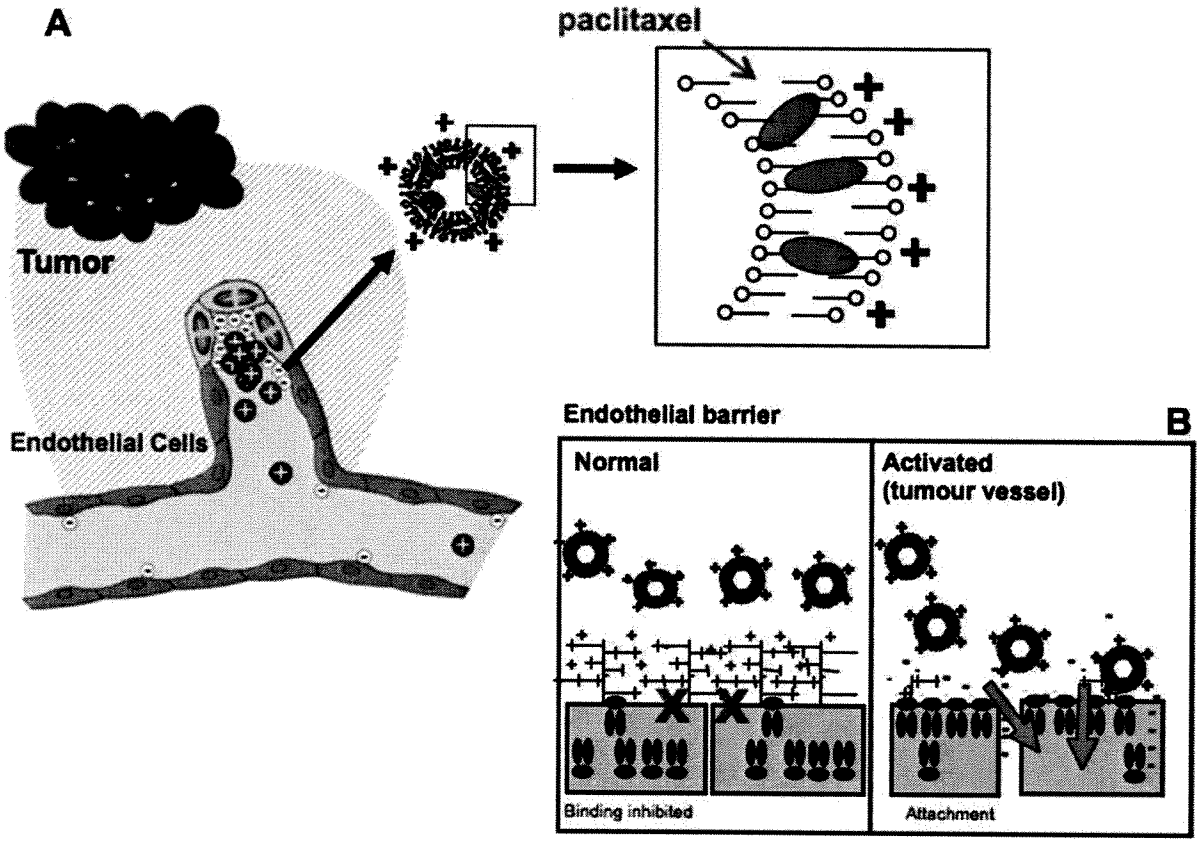

Figure 1. Mode of action of EndoTAG-1. In a simplified model of tumor cell angiogenesis (A), liposomal-embedded paclitaxel targets the vascular endothelial cells. The mechanism of selective targeting is delinated in (B). Tumor endothelial cells become negatively charged through the loss of surface glycocalix, which allows selective attachment and internalization of EndoTAG-1 impossible.

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excluded if they had a history of other malignancies within 5 years of enrollment (except for skin cancer treated locally), prior chemotherapy or radiotherapy for PDAC (except for treatment of bone metastases), major surgery within 4 weeks of enrollment or other diseases likely to interfere with study treatment or assessments.

Informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was registered with ClinicalTrials.gov, number NCT00377936. The protocol was approved by the review boards of the participating institutions and was endorsed by the 'Arbeitsgemeinschaft Internistische Onkologie' in Germany (AIO PK0104).

assessments

Patients underwent medical examination at baseline. The first treatment cycle consisted of a screening visit and a treatment phase comprising 7 weekly visits for patients in the GEM group and 14 twice-weekly visits for patients in the GEM + Endo groups. Tumor assessment was conducted according to RECIST 1.0 guidelines [21] at baseline and at the end of each treatment cycle. After termination of study treatment, patients were invited for follow-up evaluations every 8 weeks until documented disease progression. Thereafter, patient follow-up was conducted by phone until patient death. Adverse events (AEs), if applicable, were recorded at each visit and classified according to Common Terminology Criteria for Adverse Events v3.0. Quality of life and pain were self-reported by patients using the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-PAN26 questionnaires and the visual analog scale (VAS; 100 mm), respectively.

statistical analysis

This trial was exploratory and was not powered for formal superiority analysis in any end point. Sample sizes were extrapolated from comparable phase II trials in PDAC due to previous data on ET. The cut-off date for the analysis was 48 weeks after the last patient completed the first treatment cycle. All patients who were randomly assigned to the trial [intent to treat (ITT)] or received study medication [modified intent to treat (mITT)] were included in the efficacy and safety population. No individual parameter of the study was defined as primary end point. End points included overall survival (OS), progression-free survival (PFS), tumor response, quality of life, pain and the frequency and severity of AEs.

OS was defined as the time from randomization to death. Patients with no documented event (death) were censored at the date of last documented contact. Twelve-month survival rates were calculated as the number of patients still alive after 12 months from the start of treatment, of all patients with known vital status.

PFS was defined as the time from randomization to disease progression or death, whichever occurred first. Patients who discontinued prematurely for reasons other than progressive disease (PD) were censored at the date of discontinuation.

Investigator-assessed tumor response after the first treatment cycle was classified as complete response (CR), partial response (PR), stable disease (SD), or PD according to RECIST 1.0 guidelines [21]. In addition, the number of patients with disease control (CR, PR or SD) was assessed.

Other end points comprised mean changes in quality of life and pain assessment during the first treatment cycle and toxic effects. For quality of life and pain, patients were only included in the analysis if they had a baseline assessment and if at least 50% of the respective assessments during treatment were available.

Time-to-event variables were estimated using the Kaplan–Meier method. Medians and their respective 95% confidence intervals (CIs) were calculated. Cox proportional hazards models were applied to estimate the effect of the treatment group (three combination treatment groups versus GEM monotherapy) on OS and PFS stratified for ECOG PS at baseline, extent of disease (locally advanced, metastatic disease), country (Germany, Czech Republic, Hungary or Ukraine) and whether patients were enrolled according to the amended protocol allowing for continuation of treatment with study medication until disease progression. Clopper–Pearson method was used to calculate the 95% CIs for 12-month survival rates. Mean changes in quality of life and pain assessment were calculated exerting all available quality of life or pain assessments after first infusion of study medication up to the date of last infusion in the first treatment cycle and estimated together with the corresponding 95% CIs.

All tabulations of summary statistics, graphical presentations and statistical analyses were carried out by using SAS software (version 8.2) and StatXact (version 7).

results

patient characteristics

From September 2005 to June 2007, 212 chemonaive patients with advanced unresectable PDAC were randomly allocated to the trial at 32 centers in 4 countries. Twelve patients did not start treatment because of AEs in five (2.4%), withdrawal of consent in three (1.4%) and other reasons in four (1.9%) patients (Figure 2). Two hundred patients were treated with at least one dose of study medication (50 patients in each treatment group). All 212 randomized patients were included in the ITT efficacy population and all treated patients in the mITT efficacy and safety population. Baseline characteristics of the study population (Table 1) were well balanced across treatment groups, except for the ECOG PS. The number of patients with grade 2 ECOG PS was higher in the GEM + Endo treatment groups, especially for the GEM + Endo22 and GEM + Endo44 study arms. The proportion of patients with metastatic disease at baseline ranged from 76% to 84%.

treatment

Of the 200 patients treated, 158 (79%) completed the first treatment cycle (90% in GEM, 84% in GEM + Endo11, 68% in GEM + Endo22 and 74% in GEM + Endo44 group; Figure 1). The most common reasons for discontinuation during the first cycle were investigator decision in 20 (10%) patients [15 (8%) patients due to AEs] and withdrawal of consent in 14 patients (7%). Median relative dose intensity of ET was 83% in the GEM + Endo11, 87% in the GEM + Endo22 and 78% in the GEM + Endo44 arm. Correspondingly, the proportion of patients with dose delay or reduction of GEM dose tended to increase with increasing ET dose (data not shown).

An amendment allowed 80 patients of the GEM + Endo groups with clinical benefit to continue on study medication beyond the first cycle, but only 28 patients received further therapy with ET: 13 in the GEM + Endo11, 8 in the GEM + Endo22 and 7 patients in the GEM + Endo44 group. The longest treatment was achieved by one patient in the GEM + Endo22 group (five cycles completed).

efficacy

At the cut-off point for analysis, i.e. 48 weeks after the last patient completed the first treatment cycle, 161 patients had died, 39 were still alive and one patient was still receiving study medication. Median OS was 8.1 months in the GEM + Endo11, 8.7 months in the GEM + Endo22 and 9.3 months in the

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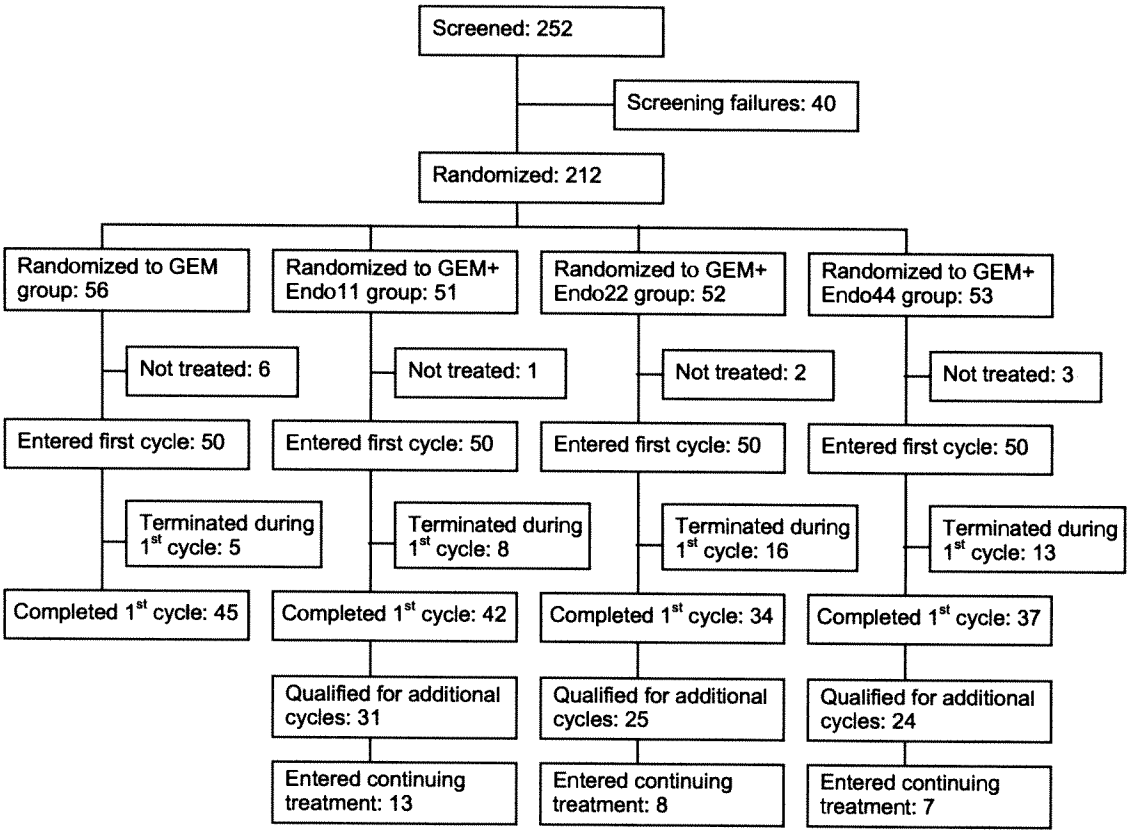

Figure 2. Study population (CONSORT diagram). CONSORT, Consolidated Standards of Reporting Trials; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel.

Table 1. Baseline characteristics of the study population

Characteristic	Treatment group (mITT population)			
	GEM (N = 50)	GEM + Endo11 (N = 50)	GEM + Endo22 (N = 50)	GEM + Endo44 (N = 50)
Sex, *n* (%)				
Male	32 (64)	34 (68)	32 (64)	33 (66)
Female	18 (36)	16 (32)	18 (36)	17 (34)
Age, years				
Median	59.5	63.0	61.0	62.5
Range	34–80	32–75	44–72	33–81
Extent of disease, *n* (%)				
Locally advanced	12 (24)	8 (16)	11 (22)	12 (24)
Metastatic	38 (76)	42 (84)	39 (78)	38 (76)
ECOG performance status, *n* (%)				
Grade 0	20 (40)	22 (44)	20 (40)	18 (36)
Grade 1	26 (52)	22 (44)	20 (40)	23 (46)
Grade 2	4 (8)	6 (12)	10 (20)	9 (18)

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; ECOG, Eastern Cooperative Oncology Group.

GEM + Endo44 arm compared with 6.8 months in the GEM group (Figure 3A). Hazard ratios (HRs) for OS relative to GEM monotherapy were 0.93 for the GEM + Endo11, 0.69 for the GEM + Endo22 and 0.66 for the GEM + Endo44 group (Table 2). Accordingly, 12-month survival rates were 21% for the GEM + Endo11, 35% for the GEM + Endo22 and 30% for the GEM + Endo44 group compared with 15% for the GEM cohort (Table 2).

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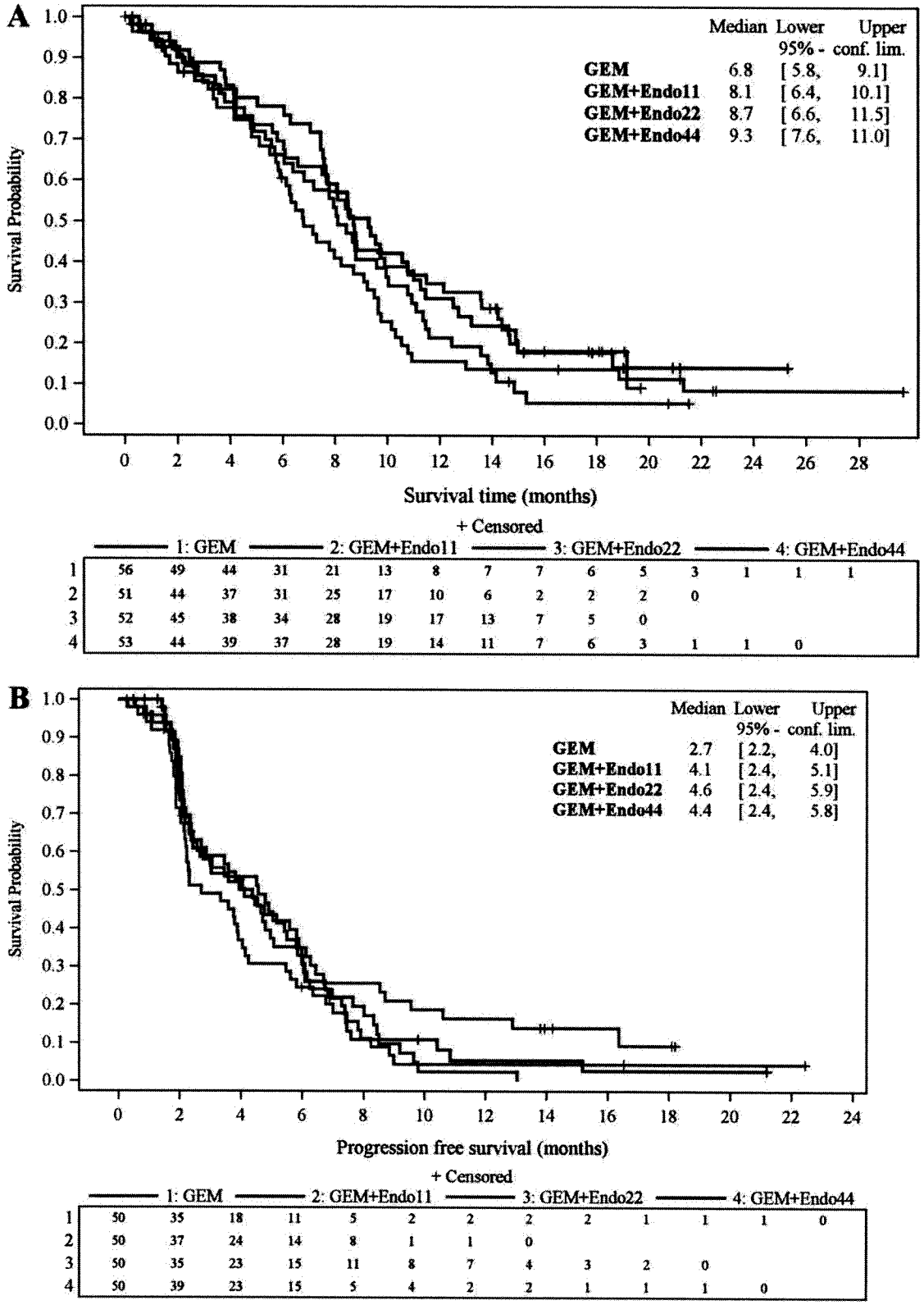

Figure 3. Kaplan–Meier curves for overall survival (A; ITT population) and progression-free survival (B; mITT population). ITT, intent to treat; mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel.

Median PFS times were longer in the GEM + Endo arms (4.1, 4.6 and 4.4 months for GEM + Endo11, GEM + Endo22 and GEM + Endo44, respectively) compared with the GEM group (2.7 months) (Figure 3B). The corresponding adjusted HRs for

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PFS were, respectively, 0.84, 0.58 and 0.74 for the GEM + Endo groups (Table 2). The 95% CIs for all survival results are listed in Table 2.

After the first cycle, tumor response according to RECIST 1.0 criteria has been measured (Table 3). PRs were similar in all study arms. However, compared with 43% of patients in the GEM group, disease control was achieved by 60%, 65% and 52% of patients in the GEM + Endo11, GEM + Endo22 and GEM + Endo44 groups, respectively.

Quality of life and pain score were evaluable in 86% and 72% of patients, respectively. Noteworthy differences in average change from baseline for QLQ-C30, QLQ-PAN26 and VAS were not observed.

Of the 200 patients treated, 56%, 42%, 50% and 54% in the GEM, GEM + Endo11, GEM + Endo22 and GEM + Endo44 groups, respectively, received second-line therapy after discontinuation of study participation at the discretion of the investigator. The most frequently used agents were GEM (38%), 5-fluorouracil (5-FU; 18%), oxaliplatin (11%), calcium folinate (9%) and capecitabine (6%); antitumor therapy agents appeared to be equally distributed across treatment groups.

safety

No unexpected toxic effects have been observed. During the first treatment cycle, severe hematological toxic effects (National Cancer Institute—Common Toxicity Criteria grade 3/4) occurred in 22%, 32% and 40% of patients in the different GEM + Endo groups (11, 22 and 44 mg/m^2, respectively) compared with 24% of the controls (Table 4). Combination of ET and GEM resulted in dose-dependent increase in grade 3/4 thrombocytopenia reaching up to 16% and 14% at the two higher dose levels, albeit without clinical symptoms or bleeding complications. At the highest ET dose level (44 mg/m^2 twice

Table 2. Survival results

	Treatment group (ITT/mITT population)			
	GEM (N = 50/50)	GEM + Endo11 (N = 50/50)	GEM + Endo22 (N = 52/50)	GEM + Endo44 (N = 53/50)
OS (ITT)				
Median (months)	6.8	8.1	8.7	9.3
OS 95% CI	5.8–9.1	6.4–10.1	6.6–11.5	7.6–11.0
HR[a]		0.93	0.69	0.66
HR 95% CI		0.60–1.43	0.44–1.07	0.43–1.03
12-month survival (ITT)				
Survival rate (%)	15	21	35	30
95% CI	6.9–28.1	10.7–35.7	21.7–49.6	17.3–44.9
PFS (mITT)				
Median (months)	2.7	4.1	4.6	4.4
PFS 95% CI	2.2–4.0	2.4–5.1	2.4–5.9	2.4–5.8
HR[a]		0.84	0.58	0.74
HR 95% CI		0.55–1.28	0.38–0.90	0.49–1.13

[a]Relative to GEM monotherapy.

ITT, intent to treat; mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; OS, overall survival; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table 3. Tumor response according to RECIST 1.0

Evaluable for response[a]	Treatment group (mITT population)			
	GEM (N = 37), n (%)	GEM + Endo11 (N = 37), n (%)	GEM + Endo22 (N = 37), n (%)	GEM + Endo44 (N = 31), n (%)
Response				
CR	0 (–)	0 (–)	0 (–)	0 (–)
PR	5 (14)	5 (14)	5 (14)	5 (16)
SD	11 (30)	17 (46)	19 (51)	11 (35)
Progressive disease	21 (57)	15 (41)	13 (35)	15 (48)
Disease control (CR + PR + SD)	16 (43)	22 (60)	24 (65)	16 (52)

[a]Reasons for nonevaluability were mainly premature termination and noncompliance with RECIST 1.0 guidelines (change of imaging method, lack of evaluable image).

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel; CR, complete response; PR, partial response; SD, stable disease.

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Table 4. Adverse events related to any study medication occurring in ≥10 patients (20%) in any individual treatment group during the first treatment cycle

Hematological disorders	48	24	40	22	50	32	66	40
Neutropenia	32	18	24	12	24	16	44	22
Anemia	20	4	8	–	14	4	32	8
Thrombocytopenia	14	2	16	8	28	16	42	14
Leukopenia	18	4	16	10	18	12	24	10
General + administration site disorders	16	4	52	4	56	12	80	40
Chills	4	–	22	–	36	–	52	16
Pyrexia	4	2	16	–	30	6	38	8
Gastrointestinal disorders	30	2	40	4	32	–	56	10
Nausea	22	–	20	–	24	–	28	6
Vomiting	12	2	16	2	10	–	30	4

mITT, modified intent to treat; GEM, gemcitabine; GEM + Endo11, gemcitabine in combination with 11 mg/m^2 liposomal paclitaxel; GEM + Endo22, gemcitabine in combination with 22 mg/m^2 liposomal paclitaxel; GEM + Endo44, gemcitabine in combination with 44 mg/m^2 liposomal paclitaxel.

weekly), increased rates of grade 3/4 neutropenia (22%) and anemia (12%) were observed.

During the first cycle, a total of seven cases of febrile neutropenia were reported in the two higher GEM + Endo dose levels, including four cases of grade 3/4. During additional cycles with GEM + Endo therapy, none was observed.

Infusion-related reactions, predominantly pyrexia and chills, were found to a higher extent in the GEM + Endo groups. The addition of ET to GEM did not increase the known liver toxicity of GEM. In the GEM+ Endo44 arm, one case of peripheral neuropathy was reported in a patient with diabetes but was considered unrelated to study medication.

AEs resulting in discontinuation of study medication were reported in four patients (8%) in the GEM + Endo11 and seven patients (14%) in each of the GEM + Endo22 and GEM + Endo44 groups. During the first cycle, two patients (4%) in each of the GEM + Endo11 and GEM + Endo22 groups and one patient (2%) in the GEM + Endo44 group died, but deaths were considered not related to study medication. During additional cycles, another two patients of the GEM + Endo11 group had severe adverse events with fatal outcome. Both events staphylococcal sepsis and death from unknown cause were considered unlikely to be related to study medication.

discussion

This phase II study examines the safety and efficacy of liposomal paclitaxel in combination with GEM in patients with advanced PDAC. The study was designed as a randomized controlled trial to select the regimen with the best risk-to-benefit ratio, most likely to succeed in phase III. Approximately 20% of patients had locally advanced PDAC and 80% had metastases, with an ECOG PS grade 0–1 in the vast majority and grade 2 in up to 20%, similar to the patient populations in other advanced PDAC trials [5, 22].

For patients with advanced PDAC, chemotherapy with GEM has been the standard therapy with an average survival of ~6 months. To improve survival, several GEM-based combination regimens, including taxanes, have been tested in the past. Only one regimen, GEM–erlotinib [5], achieved a statistically significant but modest survival benefit compared with GEM monotherapy. Meta-analyses indicate, however, that patients may benefit from GEM-based combination chemotherapies [23–25]. Recently, a combination regimen of 5-FU, folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) demonstrated a significant clinically relevant benefit in younger patients with good PS and metastatic disease [26]. In this selected patient group, median survival time increased from 6.8 to 11.1 months, with the 1-year survival rate of 48%.

At 7 weeks of treatment, our results in the GEM + Endo groups show consistent rates of disease control ranging from 52% to 65%, with median PFS between 4.1 and 4.6 months and median OS from 8.1 to 9.3 months. Even though a formal comparative analysis was not foreseen, these numbers compare well with those in the GEM arm, where the disease control rate was 43%, median PFS was 2.7 months and OS was 6.8 months, indicating a reference population with an outcome well within the range of comparable trials [5, 27]. In contrast to the trial with FOLFIRINOX, we also included patients with ECOG PS of two and locally advanced disease. Even though sample sizes are too small to allow formal subgroup analyses, we could not observe differences related to the PS but noticed that patients with locally advanced tumors may benefit most.

A similar formulation of paclitaxel, paclitaxel-loaded polymeric micelles, achieved disease control in 27 of 45 patients (60%), PFS of 2.8 months and OS of 6.5 months when given as monotherapy [11]. The formulation of paclitaxel in nanoparticles with albumin (NP) resulted in disease control in 33 of 49 patients (67%) and an OS of 9 months (preliminary results) when given in combination with GEM [8]. Both studies were conducted as single-arm trials without a control group.

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Nevertheless, the results, together with historical data from other trials [28, 29], seem to indicate an effect for the combination of taxanes with standard chemotherapy, which may be further enhanced by novel targeted therapies with a potentially better risk-to-benefit ratio.

The safety and tolerability of GEM in combination with paclitaxel is well known, with grade 3/4 hematologic toxic effects, especially neutropenia, and sensory neuropathies as major dose-limiting side-effects in 34% of the patients with non-small-cell lung cancer [30] and 70% of patients with metastatic breast cancer [31]. Combination of GEM with docetaxel resulted in grade 3/4 neutropenia in 32% of patients with advanced PDAC [28]. In the present trial, severe neutropenia occurred in 12%, 16% and 22% of patients in the different GEM + Endo groups (11, 22 and 44 mg/m^2, respectively). Grade 3/4 febrile neutropenia, which is usually of concern in combination therapies with taxanes, was observed in only four patients. No treatment-related neuropathy has been reported. This compares favorable with the trials with FOLFIRINOX or the trials investigating GPM and NP, agents with a similar chemotherapeutic backbone, where grade 3/4 neutropenia and neuropathies were frequent (FOLFIRINOX: 46% and 9%, respectively; GPM: 40% and 13.3%, respectively; NP: >20% neutropenia, no numbers for neuropathies, respectively) [8, 11], probably due to the different treatment regimens using less frequent applications at higher paclitaxel doses. The primary toxic effects of ET were infusion-related reactions associated with pyrexia or chills, mostly of mild or moderate severity, usually managed by postponement of therapy or symptomatic treatment.

There is still limited understanding of the complex modifications contributing to the aggressiveness of PDAC. Pancreatic tumors are characterized by an abundant fibrous reaction and multiple genetic alterations and epigenetic changes [32]. Attempts to develop targeted therapies, such as inhibition of metalloproteases [33] or inhibition of membrane binding of K-Ras by farnesyltransferase inhibitors [34], have largely been to no avail. Conflicting data indicate that the epidermal growth factor receptor mAb cetuximab [35] is not effective but that inhibition of its tyrosine kinase activity with erlotinib shows a moderate benefit [5]. This effect may be further increased by combination with the vascular endothelial growth factor (VEGF) inhibitor bevacizumab, which led to a nonsignificant increase in median OS from 6.0 to 7.1 months in a large phase III trial with a significant 1-month benefit in PFS (4.6 versus 3.6 months) [36]. Again, other VEGF pathway-directed agents like the oral VEGF inhibitor axitinib [37] did not meet their primary end points, indicating a complex and not well-understood role for the VEGF/vascular endothelial growth factor receptor pathway and its role for tumor microenvironment. Indeed, the abundant fibrous desmoplasia in pancreatic tumors is hypothesized to be one of the major therapeutic challenges in their treatment [38, 39]. In addition to its role as a barrier in terms of drug delivery to the tumor cells, desmoplasia may play a crucial role for tumor growth and invasion [40].

The mechanism of action of ET (Figure 1) likely involves selective targeting of the drug to tumor endothelial cells [23–25]. Since combination of GEM with ET resulted in improved survival time, it might overcome these challenges by altering vessel leakiness and thereby achieving enhanced drug delivery compared with conventional therapies [19, 20, 41, 42].

conclusions

This study indicates that ET in combination with GEM is well tolerated and may prolong survival, with dose level of 22 mg/m^2 ET achieving the best risk-to-benefit ratio. The 12-month OS rate of 35% in the whole population would be a clinically meaningful improvement if these results could be confirmed in the planned phase III trial. Because of its low toxicity, ET–GEM would be well suited as backbone for additional agents in patients who do not qualify for FOLFIRINOX.

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disclosure

JML and MPL have advisory relationships with MediGene AG. In addition, JML has received honoraria from MediGene AG. All remaining authors have declared no conflicts of interest.

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Species	Weight, kg	Est. Total Dose, mg	Dose in mg/kg	Dose in mg/m2	Est. BSA,m2
Human	70.00	20.28	0.28	11.00	1.843
Mouse	0.02	0.07	3.65	11.00	0.007
Hamster	0.03	0.10	3.18	11.00	0.009
Rat	0.15	0.28	1.86	11.00	0.025
Guinea Pig	1.00	0.98	0.98	11.00	0.089
Rabbit	2.00	1.75	0.87	11.00	0.159
Cat	2.50	2.17	0.87	11.00	0.197
Monkey	3.00	2.70	0.90	11.00	0.245
Dog	8.00	4.93	0.62	11.00	0.448

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Species	Weight, kg	Est. Total Dose, mg	Dose in mg/kg	Dose in mg/m2	Est. BSA,m2
Human	70.00	40.56	0.56	22.00	1.843
Mouse	0.02	0.15	7.29	22.00	0.007
Hamster	0.03	0.19	6.37	22.00	0.009
Rat	0.15	0.56	3.73	22.00	0.025
Guinea Pig	1.00	1.96	1.96	22.00	0.089
Rabbit	2.00	3.49	1.75	22.00	0.159
Cat	2.50	4.34	1.73	22.00	0.197
Monkey	3.00	5.40	1.80	22.00	0.245
Dog	8.00	9.86	1.23	22.00	0.448

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Species	Weight, kg	Est. Total Dose, mg	Dose in mg/kg	Dose in mg/m2	Est. BSA,m2
Human	70.00	81.11	1.13	44.00	1.843
Mouse	0.02	0.29	14.59	44.00	0.007
Hamster	0.03	0.38	12.73	44.00	0.009
Rat	0.15	1.12	7.45	44.00	0.025
Guinea Pig	1.00	3.92	3.92	44.00	0.089
Rabbit	2.00	6.98	3.49	44.00	0.159
Cat	2.50	8.67	3.47	44.00	0.197
Monkey	3.00	10.80	3.60	44.00	0.245
Dog	8.00	19.71	2.46	44.00	0.448